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RESEARCH ARTICLE



High rates of secondary non-adherence causes decreased efficacy of 0.1% topical tacrolimus in adult eczema patients: results from a multicenter clinical trial

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ABSTRACT

Background: Patients tend to apply topical medications less frequently, in improper amounts. Not only frequency but also application amount may influence treatment outcome. However, studies on relationship between application amount and objective treatment outcome have rarely been conducted.

Objective: To assess efficacy of topical agent according to application amount in adult patients, using the finger-tip unit method.

Methods: The efficacy of 0.1% topical tacrolimus in adult patients with localised atopic dermatitis was assessed using EASI, TIS, IGA, and PGA scores at baseline, follow-up. Adherence in amount was evaluated after 2 weeks of treatment using the ratio of the actual amount applied to the expected amount applied (A/E).

Results: Twenty-seven patients (20.93%) used topical tacrolimus in proper amounts (A/E: 0.8–1.2). However, 86 patients (66.67%) underused topical tacrolimus; 16 (12.40%) patients overused topical tacrolimus. Decreases in EASI scores between baseline and 2 weeks of follow-up in each group (under-amount, proper amount, over-amount) were 1.64, 4.65 and 4.21, respectively. Treatment efficacy increased in accordance with application amount. Further, TIS, IGA, PGA, VAS for Itch and DLQI scores improved concomitantly, exhibiting similar tendencies.

Conclusion: Application amount of topical agent is important in increasing treatment efficacy in adult patients with atopic dermatitis.

ABBREVIATIONS: AD: atopic dermatitis; ; BSA: body surface area; DLQI: dermatology life of quality index; EASI: eczema area and severity index; FTU: finger-tip unit; IGA: investigator global assessment; PGA: patient global assessment; TBSA: total body surface area; TIS: three-item severity; VAS: visual analogue scale

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Adherence; amount; application of topical agent; treatment efficacy

Introduction

Adherence is defined as the degree to which patients use medications as prescribed by their health care providers (1). Rates of secondary medical adherence can be studied by validated and study-specific questionnaires, no. of treatment sessions [measured in Medication Event Monitoring Systems (MEMS) monitor] and by weight (measured by weight of returned medication). Not only the frequency but also the application amount of topical medications may influence the treatment outcomes (1). However, studies to clarify the relationship between the application amount and treatment outcome objectively are rare.

Topical agents, including topical tacrolimus (Protopic®), are usually applied using the 'finger-tip unit (FTU) method'; however, the efficacy of this method has not been validated by clinical studies.

According to our previous study on topical adherence, Korean patients with eczema tend to apply topical tacrolimus less frequently and in inappropriate amounts (2). Herein, we assessed the

efficacy of topical tacrolimus according to the amount applied (adherence) among Korean patients with localised atopic dermatitis (AD) and investigated further the relationship between adherence of the amount applied and objective treatment outcome.

Material and methods

Study population and study design

The present study (phase IV pharmaceutical trial using topical tacrolimus) was conducted from September 2013 to May 2016. Detailed inclusion criteria were as follows: adult patients (aged ≥19 years) diagnosed with AD [body surface area (BSA) <5%] and prescribed with 0.1% topical tacrolimus. Patients who were prescribed with other systemic agents, including antihistamines, or other topical agents, including emollients during the study period, were excluded. Patients lost to follow-up, such as those who did not bring the remaining topical tacrolimus at the first or second visit day and patients not adhering to the application frequency

(checked by patient reporting) were also excluded from the final analysis.

The investigation was performed on a multi-centre basis. Overall, six tertiary medical centres that cover the southeast part of the Korea in geographics and ~8 millions people in population, including Pusan National University Hospital, Pusan National University Yangsan Hospital, Busan Paik Hospital, Ulsan University Hospital, Maryknoll Medical Centre, and Haeundae Paik Hospital in the Republic of Korea participated in the study. This study was approved by the Institutional Review Boards of each institution, and the signed consent was acquired from patients explaining purpose of the trial.

At baseline, the site of AD was identified, and the size of the lesion was measured using the rule of the palms (one palm considered as 1% BSA). In terms of the application amount, the patients were instructed to apply 500 mg (1 FTU) of 0.1% tacrolimus ointment per 2% of the total BSA (TBSA) (proper amount; amount that should be used). In terms of the frequency of application, they were instructed to apply tacrolimus twice daily. The Eczema Area and Severity Index (EASI), Three-Item Severity (TIS), Investigator Global Assessment (IGA), Patient Global Assessment (PGA), Visual Analogue Scale (VAS) for Itch, and Dermatology Life of Quality Index (DLQI) scores were used to determine the treatment efficacy at baseline and during the follow-up period (3–6). The TIS scores were assessed in three aspects, namely, redness, excoriation/papule, and oedema. Investigator- and patient-assessed AD severities were recorded on a five-point scale: very mild, mild, moderate, severe, and very severe (IGA and PGA scores).

Follow-up visits were conducted at 1 and 2 weeks of treatment, and the number and amount of applications of topical tacrolimus were checked during the visit. The total amount of application was measured using the difference in the weight of each ointment between baseline and after 2 weeks of follow-up. Adherence to the amount of agent applied was evaluated using the ratio of the actual amount applied to the expected amount applied (A/E) after 2 weeks of follow-up. The expected amount applied was calculated as follows: 250 mg (0.5 FTU) multiplied by the size of the eczema as the percentage of TBSA (%TBSA) multiplied by the total number of applications in 2 weeks. The applied amount was considered proper if the A/E ratio was between 0.8 and 1.2. The scales on the treatment efficacy, such as the EASI, TIS, IGA, PGA, VAS, and DLQI were assessed again during the follow-up visits, and the differences between the baseline and

follow-up values would show the efficacy of the topical medication used. The differences in these values between the three groups were compared to investigate the relationship between the application amount and treatment efficacy.

Statistical analysis

All statistical analyses were performed using the IBM SPSS (IBM® SPSS® Statistics, IBM Corporation, NY, USA) version 21. We used the Pearson’s chi-squared test and Fisher’s exact test for the analysis of categorical variables and the one-way analysis of variance (ANOVA) and Kruskal–Wallis test for the analysis of continuous variables. The ANCOVA test was adopted for the adjustment of differences of the baseline variables (age, disease duration, BSA, lesional location). A Pearson correlation analysis was conducted to evaluate the differences among the three groups divided by the A/E ratio on the treatment efficacy scales (EASI, TIS, IGA, PGA, VAS, and DLQI). *p* values < 0.05 were considered statistically significant.

Results

Two hundred fifty-four patients were enrolled from six centres; however, 125 patients were excluded owing to follow-up loss (84 patients), atypical lesions (24 patients), and non-adherence in terms of application frequency (17 patients). A total of 129 patients (48 men and 81 women; male to female sex ratio, 1:1.70) were enrolled in the study (Figure 1). The mean age of the patients was 40.52 years, and the average lesion size was 2.05% of the TBSA with a span of 0.5 to 5. The patient demographics are summarised in Table 1.

The lesions were distributed on various sites. The face and neck were the most common sites of involvement (53, 41.09%), followed by the arms, including the antecubital fossa (14, 10.85%). Multiple involvements were also common (27, 20.93%). The distribution of the lesions is listed in Table 2.

The average A/E ratio in all patients was 0.76. Twenty-seven patients with AD (20.93%) used topical tacrolimus in proper

Table 1. Patient demographics.

Total number of patients	<i>N</i> = 129
Mean age (years)	40.52
Male:female	48:81 (1:1.70)
Application area (BSA, %)	2.05 (0.5–5)

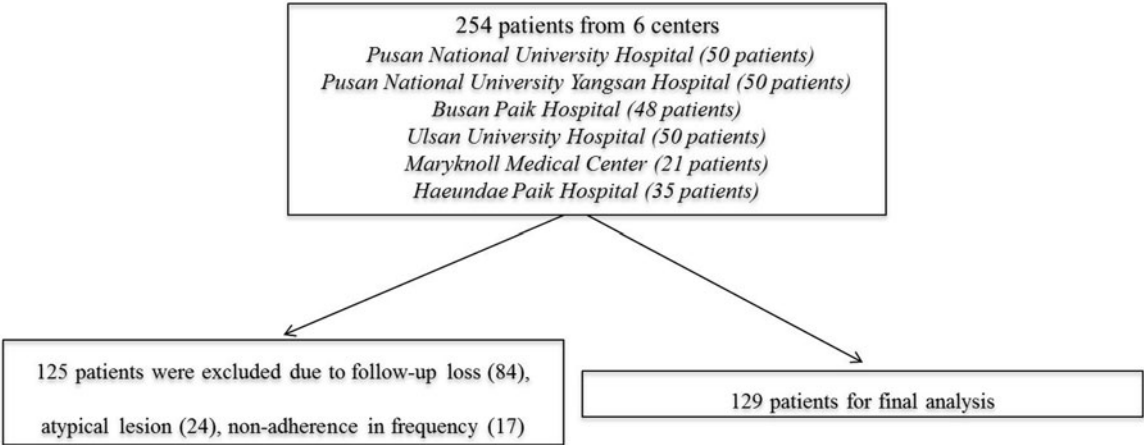


Figure 1. Patients enrolment.

Table 2. Clinical characteristics of the three subgroups (under, proper and over-amount group).

	Under-amount group ^a , <80%	Proper amount group ^b , 80–120%	Over-amount group ^c , >120%	<i>p</i> value
Male:female	32:54	11:16	5:11	.688
Mean age (years, SD)	37.93 (16.24)	44.68 (16.49)	47.88 (18.79)	.042
Mean disease duration (months, SD)	28.06 (56.92)	17.02 (26.91)	18.12 (19.18)	.694
Mean BSA (% , SD)	2.29 (1.54)	1.69 (0.81)	1.32 (0.64)	.008
Lesional location (%)				
Head and neck	43 (50.00)	14 (51.85)	6 (37.50)	.219
Trunk	3 (3.49)	2 (7.41)	1 (6.25)	
Extremity	19 (22.09)	9 (33.33)	5 (31.25)	
Multiple involvement	21 (24.42)	2 (7.41)	4 (25.00)	

^aUnder-amount group: <0.8 in the ratio of actual amount applied to expected amount applied (A/E) estimated after 2 weeks of follow-up.

^bProper amount group: 0.8–1.2 in the ratio of actual amount applied to expected amount applied (A/E) estimated after 2 weeks of follow-up.

^cOver-amount group: >1.2 in the ratio of actual amount applied to expected amount applied (A/E) estimated after 2 weeks of follow-up.

Table 3. Amount of application of topical tacrolimus 0.1%.

	Mean actual amount applied	Number of patients (%)
Under-amount group ^a , <80%	49.45%	86 (66.67)
Proper amount group ^b , 80–120%	96.10%	27 (20.93)
Over-amount group ^c , >120%	192.65%	16 (12.40)
Total	76.03%	129 (100)

^aUnder-amount group: <0.8 in the ratio of actual amount applied to expected amount applied (A/E) estimated after 2 weeks of follow-up.

^bProper amount group: 0.8–1.2 in the ratio of actual amount applied to expected amount applied (A/E) estimated after 2 weeks of follow-up.

^cOver-amount group: >1.2 in the ratio of actual amount applied to expected amount applied (A/E) estimated after 2 weeks of follow-up.

amounts (A/E: 0.8–1.2). However, 86 patients with AD (66.67%) underused topical tacrolimus (A/E < 0.8); 16 (12.40%) patients overused topical tacrolimus (A/E > 1.2). The amount of application according to the three groups is summarised in Table 3.

As the main results of the present study, the treatment efficacies according to the three groups (under-amount group, proper amount group, and over-amount groups) were assessed using the multiple variables, including the EASI, TIS, IGA, PGA, VAS for Itch, and DLQI scores.

In terms of the EASI score, the mean baseline value of the total 129 patients was 5.60. The under-amount group showed a mean value of 5.51 at baseline. The proper amount group and over-amount group had a mean baseline value of 5.75 and 5.85, respectively. The baseline values among the three groups did not exhibit statistically significant differences. After 2 weeks of follow-up, the EASI scores decreased to 3.02 in total, to 3.87 in the under-amount group, to 1.09 in the proper amount group, and to 1.65 in the over-amount group. The total patients and the under-amount, proper amount, and over-amount groups had a mean difference value of 2.58, 1.64, 4.65, and 4.21, respectively, between the baseline and 2 weeks of follow-up. The proper amount group (4.65) and over-amount group (4.21) showed more significant changes in the EASI score than the under-amount group (1.64) with a statistical significance. The values between the proper amount group (4.65) and over-amount group (4.21) did not exhibit statistically significant differences (Figure 2(A)).

The TIS (redness, excoriation/papule, and oedema), IGA, PGA, VAS for Itch, and DLQI scores for evaluating the treatment efficacy had similar tendencies showing that the proper amount group and over-amount group had more significant changes in each score than the under-amount group. The changes in the values over 2 weeks between the proper amount group and over-amount group did not exhibit statistically significant differences in each score (Figure 2(B–H)). The detailed values of each score are presented in Table 4.

Discussion

Adherence to topical agents is relatively poorer than that to oral medications (7). The topical adherence rate in patients with psoriasis was reported to be between 55 and 100% in terms of frequency and between 35 and 72% in terms of the applied amount of topical agents, according to a previous study (8). In our previous study on the adherence to topical medications in Korean patients, compliance in terms of application frequency was 59.0%; in terms of the application amount, only 16.0% of the patients actually used a proper amount (2); the remaining patients applied either too much or too little of the topical agent. We could determine through our previous study and other numerous previous reports that adherence to the recommended amounts of topical agents is especially low and that the amount used is actually extremely variable among patients (2,7,9,10).

However, studies on the relationship between the application amount and treatment outcome are rare. Considering the purpose of topical medications, that is, clinical improvement, studies not only on the adherence itself but also on the relationship between adherence and treatment outcome are needed to obtain more evidence in the clinical practice.

The FTU method is frequently used in daily clinical practice when instructing patients on the amount of topical medications that should be used (11). Originally, FTU was introduced by the concept that patients usually squeeze topical agents from a tube held in one hand onto the fingertip of the opposite hand, usually onto the index finger (12). The use of FTU has some inaccuracies and variabilities (13) but has the advantage of being easily understandable and used to both patients and medical personnel. This simple method has a potential in ensuring that patients do not use insufficient or excessive amounts of topical medications and should also help dermatologists prescribe proper amounts of topical agents.

Our study was designed on the basis of this FTU method. We instructed the enrolled patients to use the topical medications based on the criteria of this method; the three groups (under-amount, proper amount, over-amount) were also classified in accordance with the ratio of the actual amount of topical agents used to the expected amount of agents calculated using the FTU.

In general, the efficacy increased in accordance with the application amount of topical tacrolimus in terms of the EASI, TIS, IGA, PGA, VAS for Itch, and DLQI scores. According to our results, the proper amount group and over-amount group showed a greater decrease in the EASI score over 2 weeks than the under-amount group; further, there was no statistically significant difference between the changes in the proper amount group and over-amount group. This tendency (proper amount group = over-

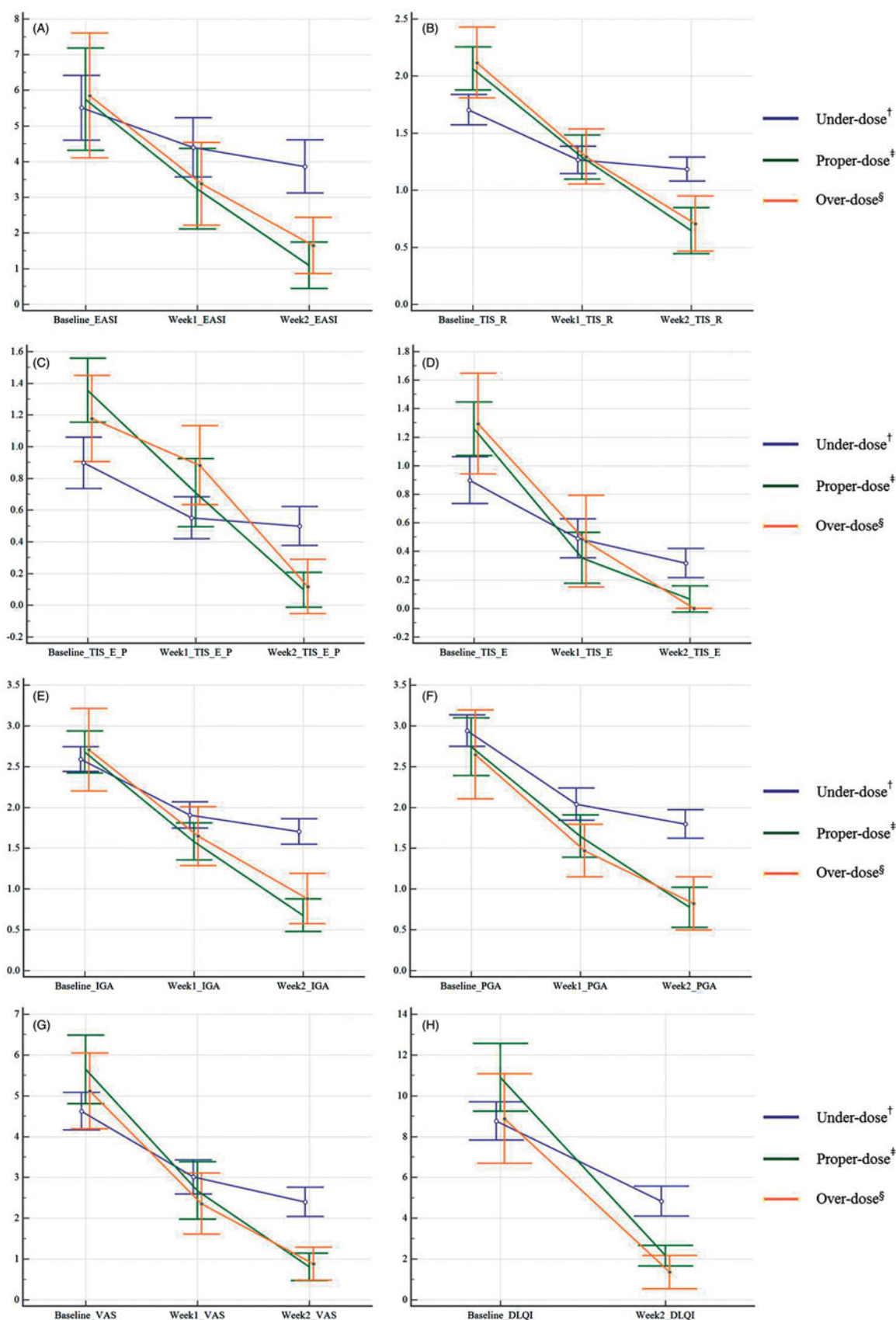


Figure 2. Efficacy assessment according to the amount of application of topical tacrolimus 0.1%. (A) EASI, (B) TIS-redness, (C) TIS-excoriation/papule, (D) TIS-edema, (E) IGA, (F) PGA, (G) VAS for itch, (H) DLQI. [†]Under-amount group: <0.8 in the ratio of actual amount applied to expected amount applied (A/E) estimated after 2 weeks of follow-up. [‡]Proper amount group: $0.8\text{--}1.2$ in the ratio of actual amount applied to expected amount applied (A/E) estimated after 2 weeks of follow-up. [§]Over-amount group: >1.2 in the ratio of actual amount applied to expected amount applied (A/E) estimated after 2 weeks of follow-up.

Table 4. Efficacy score according to the amount of application of topical tacrolimus 0.1%.

	Difference -between baseline and Week 2	Under-amount ^a , <80% (mean, SD)	Proper amount ^b , 80–120% (mean, SD)	Over-amount ^c , >120% (mean, SD)	<i>p</i> value	95% confidence intervals ^d
EASI	Baseline	5.51 ± 4.51	5.75 ± 3.91	5.85 ± 3.40	.484	(2.26, 3.28)
	Week 1	4.40 ± 4.13	3.24 ± 3.08	3.38 ± 2.25	.482	
	Week 2	3.87 ± 3.73	1.09 ± 1.78	1.65 ± 1.54	<.05	
	Difference	1.64 ± 1.31	4.65 ± 2.61	4.21 ± 2.05	<.05	
TIS-redness	Baseline	1.70 ± 0.66	2.06 ± 0.51	2.12 ± 0.60	<.05	(0.33, 0.72)
	Week 1	1.27 ± 0.60	1.29 ± 0.53	1.29 ± 0.47	.906	
	Week 2	1.18 ± 0.52	0.65 ± 0.55	0.71 ± 0.47	<.05	
	Difference	0.52 ± 0.65	1.42 ± 0.50	1.41 ± 0.62	<.05	
TIS-excoriation/papule	Baseline	0.90 ± 0.81	1.35 ± 0.55	1.18 ± 0.53	<.05	(0.30, 0.67)
	Week 1	0.55 ± 0.66	0.71 ± 0.59	0.88 ± 0.49	<.05	
	Week 2	0.50 ± 0.61	0.10 ± 0.30	0.12 ± 0.33	<.05	
	Difference	0.40 ± 0.64	1.26 ± 0.51	1.06 ± 0.56	<.05	
TIS-edema	Baseline	0.90 ± 0.82	1.26 ± 0.51	1.29 ± 0.69	<.05	(0.15, 0.44)
	Week 1	0.49 ± 0.68	0.35 ± 0.49	0.47 ± 0.62	.782	
	Week 2	0.32 ± 0.51	0.06 ± 0.25	0.00 ± 0.00	<.05	
	Difference	0.58 ± 0.61	1.19 ± 0.48	1.29 ± 0.69	<.05	
IGA	Baseline	2.59 ± 0.76	2.68 ± 0.70	2.71 ± 0.99	.746	(0.70, 1.20)
	Week 1	1.91 ± 0.80	1.58 ± 0.62	1.65 ± 0.70	.107	
	Week 2	1.70 ± 0.79	0.68 ± 0.54	0.88 ± 0.60	<.05	
	Difference	0.89 ± 0.73	2.00 ± 0.68	1.82 ± 0.95	<.05	
PGA	Baseline	2.94 ± 0.96	2.74 ± 0.96	2.65 ± 1.06	.328	(0.52, 1.10)
	Week 1	2.04 ± 0.98	1.65 ± 0.71	1.47 ± 0.62	<.05	
	Week 2	1.80 ± 0.87	0.77 ± 0.67	0.82 ± 0.64	<.05	
	Difference	1.14 ± 0.95	1.97 ± 0.80	1.82 ± 0.81	<.05	
VAS	Baseline	4.62 ± 2.30	5.65 ± 2.30	5.12 ± 1.80	.120	(1.22, 2.27)
	Week 1	3.01 ± 2.09	2.68 ± 1.92	2.35 ± 1.46	.506	
	Week 2	2.40 ± 1.78	0.81 ± 0.91	0.88 ± 0.78	<.05	
	Difference	2.22 ± 1.57	4.84 ± 2.27	4.24 ± 1.56	<.05	
DLQI	Baseline	8.77 ± 4.71	10.90 ± 4.55	8.88 ± 4.28	.069	(2.49, 4.21)
	Week 2	4.83 ± 3.65	2.16 ± 1.37	1.35 ± 1.58	<.05	
	Difference	3.94 ± 2.48	8.74 ± 4.01	7.53 ± 3.34	<.05	

^aUnder-amount group: <0.8 in the ratio of actual amount applied to expected amount applied (A/E) estimated after 2 weeks of follow-up.

^bProper amount group: 0.8–1.2 in the ratio of actual amount applied to expected amount applied (A/E) estimated after 2 weeks of follow-up.

^cOver-amount group: >1.2 in the ratio of actual amount applied to expected amount applied (A/E) estimated after 2 weeks of follow-up.

^dAdjusted for age, disease duration, BSA, lesional location.

amount group > under-amount group) was presented also in other treatment efficacy scores, such as the TIS (redness, excoriation/papule, and oedema), IGA, PGA, VAS for Itch, and DLQI scores. This means that an optimal application of topical medications instructed using the FTU method is important. Considering the higher proportions in the under-amount group with about two-thirds in total, treatment failure in patients with topical medications is considerably dependent on low adherence by patients in terms of the application amount using the FTU method.

The over-amount group did not exhibit better treatment outcomes than the proper amount group, indicating the unnecessary excessive use of topical agents with expectations of a rapid effect. The patients in the over-amount group in the present study did not adhere to the instructions with their expectation of a rapid effect (unpublished data). However, regarding the similar treatment outcomes in the proper amount group and over-amount group, excessive usage of topical medications is only a problem of wasting unnecessary amounts of a drug, rather than a significant problem as in the low treatment efficacy in the under-amount group.

Our study has limitations in several aspects. We classified the study population using an A/E ratio from 0.8 to 1.2, according to our previous study on the topical adherence itself (2). Similar to other studies, relatively dominant portions of the patients were classified into the under-amount group, which was approximately two-thirds in our present study (7,14). According to our purpose in terms of the relationship between the amount of topical medication used and the treatment efficacy, we classified the study population by the ratio of the actual amount used to the

expected amount that should be used. Thus, many determinants of medical non-adherence such as severity of AD, smoking status, etc. might have been potential confounders to the results from this study.

Conclusion

Treatment efficacy increased in accordance with application amount (proper amount group = over-amount group > under-amount group). Based on results from this study, we recommend the physicians to emphasise medical adherence in the aspect of application amount to reduce treatment failure in patients with topical medication.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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